Hereditary hyperparathyroidism

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Summary

Primary hyperparathyroidism is an endocrine disorder featured by an excessive and unregulated secretion of parathyroid hormone from one or more parathyroid glands. Generally, it can occur at any age, but it is seen most commonly in the sixth decade of life. It represents a rare endocrine disease in children and young adults and its occurrence in these subjects strongly suggest the possibility of facing a hyperparathyroidism familial syndrome. Molecular genetics have provided new acquisitions on parathyroid tumorigenesis in the last decade. Mutations in specific genes have been demonstrated to account for the parathyroid tissue outgrowth. The availability of specific DNA testing has improved diagnostic accuracy and simplified family monitoring in many cases. Here, a brief review on clinical, pathological and genetic aspects of primary hyperparathyroidism in the setting of hereditary forms of the disease is treated.

KEY WORDS: primary hyperparathyroidism, hypercalcemia, hereditary hyperparathyroidism, clinical management, DNA testing.

Introduction

Primary hyperparathyroidism (PHPT) is a disorder featured by an excessive and unregulated secretion of parathyroid hormone (PTH) from one or more parathyroid glands. Clinical diagnosis relies on the two major biochemical hallmarks of the disease: hypercalcemia and elevated circulating concentrations of PTH. Generally, PHPT can occur at any age, but it is seen most commonly in the sixth decade of life. Overall, PHPT has a prevalence of 3/1000 in the general population (1). The female:male ratio has been reported to be 3:1 and women may exhibit PHPT clinical expression in the first menopausal decade, between 50 and 60 years (2). PTH hypersecretion is generally determined by one or more parathyroid glands and the most frequent histopathological picture accounting for PHPT is represented by a solitary benign adenoma, nearly 80% of cases, and less frequently multiple adenomas, hyperplasia of all parathyroid glands, observed in 15-20% of PHPT patients, and carcinoma occur. The latter represents no more than 0.5% of PHPT cases (3). PHPT, usually, is a rare endocrine disease in children and young adults and when present in these subjects is quite always in the context of a hyperparathyroidism familial syndrome. Contrarily to sporadic PHPT, parathyroid hyperplasia is commonly associated to hereditary forms of PHPT, such as Multiple Endocrine Neoplasia type 1 (MEN1) and type 2 (MEN2) syndromes, Familial Isolated Hyperparathyroidism syndrome (FIHPT), Hyperparathyroidism-Jaw tumors syndrome (HPT-JT), Familial Hypocalciuria Hypercalcemia (FHH) syndrome, Neonatal Severe Hyperparathyroidism (NSHPT) syndrome and Autosomal Dominant Moderate hyperparathyroidism (ADMH) syndrome (Table I).
New important molecular insights on parathyroid tumorigenesis have been acquired in the last decade. This is particularly true for hereditary forms of primary hyperparathyroidism where mutations in specific genes, mainly anti-oncogenes, account for the parathyroid tissue outgrowth.

Pathophysiological aspects of PHPT

Molecular genetic studies contributed to unravel a wide spectrum of molecular mechanisms underlying parathyroid tumorigenesis. PHPT pathophysiology can be briefly summarized as it follows:

1. Disorder of cell proliferation rate caused by alterations of several genetic mechanisms with clonal loss or gain of cell function, as clearly demonstrated by molecular genetic studies (4).
2. Disorder of the extracellular calcium-dependent set-point that causes the loss of the normal feedback control on PTH production and secretion by extracellular calcium concentrations (5).

Finally, a past history of external neck irradiation in childhood should also be taken into consideration (6).
Differently from other endocrine tumors, such as pituitary and thyroid neoplasms, parathyroid abnormal growth does not compress the nearby tissues, partly explaining the asympto-

Table I - Clinical syndromes of familial forms of primary hyperparathyroidism.

Multiple Endocrine Neoplasia type 1 (MEN1)
Multiple Endocrine Neoplasia type 2A (MEN2A)
Familial Isolated Primary hyperparathyroidism (FIHPT)
Hyperparathyroidism- Jaw tumors (HPT-JT)
Familial Hypocalciuric Hypercalcemia (FHH)/Neonatal Severe Hyperparathyroidism (NSHPT)
Autosomal Dominant Moderate Hyperparathyroidism (ADMH)

matic outcome of PHPT for several years before diagnosis.

Genetic aspects in familial forms of PHPT

Molecular genetics strongly contributed to clearly evidence that PHPT may also occur as a familial cluster (Table I). In Table II familial hyperparathyroid disorders with their main genetic features are briefly summarized. In any case, each of the following described syndromes should be clinically approached through a differential diagnosis. In deed, a differential diagnosis will include an integrating approach to all the hereditary forms of PHPT.

MEN1

MEN1 (OMIM 131100) is a complex tumor-predisposing disorder inherited in an autosomal dominant manner with a high degree of penetrance, nearly 100% within 50 years of age. The syndrome exhibits a high grade of clinical variability, also in members from the same affected family. More than 20 combinations of both endocrine and nonendocrine tumors have been reported in MEN1 patients, with three endocrine localizations constituting the "typical" clinical features of this syndrome: multiple tumors of parathyroid glands (generally all the parathyroid glands), pituitary adenomas and tumors of the neuroendocrine cells in the gastroenteric tract (7). Advances in molecular biology and genetics have led to the identification of the specific genetic defect, at chromosome 11q13 (Table II), improving the understanding and ability to early diagnosis this syndrome (8).

MEN1-associated PHPT

MEN1-PHPT represents the most common endocrinopathy associated to MEN1 syndrome, accounting for the 2-4% of global PHPT forms and it represents the first clinical expression of MEN1 syndrome in approximately 90% of individuals (7). It does not exhibit sex prevalence and its age onset is typically between 20 and 25 years (Table II), three decades earlier than the sporadic cases of PHPT (9, 10). Its penetrance reaches 100% with age and all MEN1 affected individuals are expected to have hypercalcemia by age 50 years.

MEN1-PHPT is often mild and asymptomatic with biochemical evidence of hypercalcemia often detected in the course of evaluation of individuals known to have or be at risk for MEN1 syndrome. However, even if the MEN1-associated PHPT is frequently asymptomatic for a long period of time, a reduced bone mass can be observed in hyperparathyroid women as early as 35 years of age (11).

The common clinical manifestations of hypercalcemia are similar to those observed in nonhereditary sporadic form of PHPT. However, it must be taken into account that hypercalcemia may increase the secretion of gastrin from a gastrinoma, precipitating and/or exacerbating symptoms of Zollinger-Ellison syndrome, a clinical picture frequently associated to MEN1 syndrome (10).

Pathology

MEN1 affected subjects generally exhibit a multiglandular parathyroid disease with the enlargement of all the parathyroid glands, rather than a single adenoma (Table II); they are considered to be tumors of clonal origin (10). Asymmetric and asynchronic parathyroid outgrowth involves all parathyroid glands in these patients and after 8-10 years from sub-total parathyroidectomy a 50% of recurrence of PHPT has been observed. This could be due to an onset of a new tumor in the context of the parathyroid tissue remnant or, alternatively, to the growth of an unremoved tumor (10). Malignant progression of parathyroid tumors is not a clinical feature observed in "classic" MEN1 syndrome.

Molecular aspects

Germline inactivating mutations of *MEN1* gene have been found in most of the affected from MEN1 kindreds (Table II). Recent advances on pathophysiological roles of menin, the protein product of *MEN1* gene, disclose the existence of an intricate network composed by several molecular partners interacting with menin: Smad3, TGFβ, JUND, GFAP, vimentin, NF-kB, NM23H1, ERK, JUNK, Elk-1 and c-Fos (12-24). However, it is still completely unknown how mutations in menin cause tumorigenesis, nor is the function of menin. Menin may play different roles in different tissues interacting with such different proteins, but also the interacting proteins of such a molecular network may have a role in both the onset and progression of MEN1-associated tumors.

However, MEN1 parathyroid tumorigenesis has been widely

Table II - Chromosomal localization and genetic defects underlying each familial form of hereditary hyperparathyroidism.

Syndrome/OMIM#°	Chromosomal localization	Gene/activity	Type of germline mutation
MEN1/131100	11q13	*MEN1*/oncosoppressor	Inactivating
MEN2A/171400	10q11.1	*RET*/proto-oncogene	Activating
FIHPT/145000	11q13*, 1q25-q31*, 3q13.3-q21*, and still unknown loci	*MEN1*/oncosoppressor, *HRPT2*/oncosoppressor, *CaSR*/GPCR and still unknown genes	Inactivating for *MEN1*, *HRPT2*, and *CaSR* genes
HPT-JT/607393	1q25-q31	*HRPT2*/oncosoppressor	Inactivating
FHH-NSHPT/145980-239200	3q13.3-q21	*CaSR*/GPCR	Inactivating
ADMH/601199	3q13.3-q21	*CaSR*/GPCR	Atypical inactivating

° OMIM: Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=omim)

* Only a subset of families affected by FIHPT map to 11q13, or 1q25-q31, or 3q13.3-q21 loci. Mutations have been described in *MEN1*, *HRPT2* and *CaSR* genes.

demonstrated to progress through the inactivation of the "wild type" allele of *MEN1* gene, a tumor suppressor gene, at somatic level indirectly evidenced as loss of heterozygosity (LOH) at 11q13 or intragenic DNA markers (25-27). After the cloning of *MEN1* gene the early detection of asymptomatic carriers dramatically decreases the morbidity and mortality of MEN1 syndrome, providing the opportunity to initiate appropriate treatment at early stages.

Treatment of MEN1-PHPT manifestations

Neck surgery still represents the elective treatment of this form of PHTP. However, the use of bone anti-resorptive agents should be considered prior to surgery, in order to both reduce hypercalcemia and limit PTH-dependent bone resorption.
No general consensus has been reached on which technique could be the optimal surgical approach in MEN1-associated PHPT. It may be treated with either subtotal parathyroidectomy (removal of 7/8 of the parathyroid tissue) or cryopreservation of parathyroid tissue or total parathyroidectomy and autotransplantation of parathyroid tissue (28) (Table III). As above mentioned, it has been determined that eight to twelve years after successful subtotal parathyroidectomy, PHPT recurred in as many as 50% of euparathyroid individuals with MEN1 syndrome (10), likely as the result of either new neoplasia arising in residual normal tissue, or neoplasia progressing in the residual tissue. Elaraj et al. (29) showed that subtotal and total parathyroidectomy resulted in longer recurrence-free intervals compared with lesser resection. Cumulative recurrence rates for procedures considering a less than subtotal parathyroid resection were 8%, 31%, and 63% at one, five, and ten years, respectively, while for more extensive parathyroid resection, subtotal or total, the cumulative recurrence rates were 0%, 20%, and 39% at one, five, and ten years, respectively. Severe hypoparathyroidism exhibits a higher incidence after total parathyroidectomy, supporting the use of subtotal parathyroidectomy as the initial procedure of choice in MEN1 syndrome (29). Biochemical assessment of serum concentration of PTH on the first day following subtotal or total parathyroidectomy may result as a good predictor of residual parathyroid function (30, 31). However, repeated measurements of serum calcium concentration are also useful and less expensive than measurement of the serum concentration of PTH (30).
If auto-transplantation of the parathyroid glands has been performed, the serum concentration of PTH should be assessed no earlier than two months post-operatively and then once a year thereafter; serum concentration of PTH should be measured in separate, but simultaneous, blood samples, one from the arm without and one from the arm with the parathyroid tissue auto-transplantation. This procedure allows the physician both to assess the function of the transplanted parathyroid tissue and monitor for possible recurrence of hyperparathyroidism. Postoperative parathyroid localizing studies may be helpful if hyperparathyroidism recurs.

Multiple Endocrine Neoplasia type 2A syndrome (MEN 2A)

MEN2A is a clinical variant of MEN2 syndrome (OMIM 171400) and it specifically carries an increased risk for parathyroid adenoma or hyperplasia (Table I). Similarly to MEN1 also this syndrome is inherited in an autosomal dominant manner with a high degree of penetrance and clinical variability. MEN2A variant is clinically characterized by the occurrence of medullary thyroid carcinoma (MTC), nearly in the 100% of affected sub-

Table III - Main clinical features of various forms of hereditary hyperparathyroidism.

Syndrome	Age of onset (yr)	Parathyroid glands involvement	Pathology	Treatment
MEN1	20-25	Multiglandular	Hyperplasia/ Adenoma(s)	SPTX or TPTX with autologous reimplantation + transcervical thymectomy
MEN2A	>30	Single/ Multiglandular	Multiple adenomas/ Hyperplasia	Resection of only enlarged glands, SPTX, TPTX with autologous reimplantation
FIHPT	N. R.	Single/ Multiglandular	Single, Multiple adenoma(s)	Single disease: parathyroid adenomectomy Multiglandular disease: SPTX or TPTX with autologous reimplantation
HPT-JT	>30 [(average age 32 (ref. 28)]	Single/ Multiglandular (generally two glands)	Single or double adenoma (cystic parathyroid adenomatosis). Parathyroid carcinoma in approximately 10-15% of affected individuals	Single disease: parathyroid adenomectomy Multiglandular disease: SPTX or TPTX with autologous reimplantation. Carcinoma: Neck surgery, specifically an en bloc resection of primary tumor, as the only curative treatment
FHH/NSHPT	All ages/ at birth or within the first 6 months	Multiglandular	Mildly enlarged parathyroid glands/Markedly hyperplastic parathyroid glands	FHH: patients do not benefit from surgery of parathyroid lesions, but subtotal parathyroidectomy can be performed in subjects developing symptomatic PHPT NSHPT: TPTX
ADMH	44.5±3.9 (ref. 99)	Single/ Multiglandular	Diffuse to nodular parathyroid neoplasia	Radical subtotal parathyroid resection with parathyroid remnants of 10-20 mg or TPTX with autologous reimplantation

Legend: SPTX=Subtotal parathyroidectomy; TPTX=Total parathyroidectomy.

jects, pheochromocytoma, bilateral or unilateral, in 50% of patients, whereas the PHPT is described in 20-30% of MEN2A cases (7).

MEN2A-associated PHPT

PHPT in MEN2A is less common than in MEN1 syndrome, occurring in 20 to 30% of the patients (7).
MEN2A-associated PHPT may silently occur for several decades. It is sustained by the presence by multiple adenomas or, less frequently, parathyroid hyperplasia and it exhibits a less aggressive behavior respect to the MEN1-associated PHPT, usually occurring after the third decade (53-56) (Table II). Generally, MEN 2A-related HPT is also mild and asymptomatic, with approximately 15-25% of the patients developing clinical signs of their disease (57-59).
As usual, the diagnosis of parathyroid abnormalities is made when biochemical screening reveals simultaneously elevated serum concentrations of calcium and PTH (60).
Annual biochemical screening is recommended in case of affected individuals who have not had parathyroidectomy and auto-transplantation (61). Moreover, it has been suggested that only individuals with codon 634 mutations undergo annual screening and that individuals carrying other mutations may be screened every two to three years (7).

Pathology

MEN2A-PHPT is generally sustained by a single enlarged parathyroid gland, although multiglandular neoplasia does occur, with single or multiple parathyroid adenomas, respectively, or, less frequently, parathyroid hyperplasia (Table III).

Molecular aspects

RET proto-oncogene is the responsible gene (62) (Table II). The most frequent activating germline mutations associated with MEN2A-PHPT phenotype occur at the exon 11 level, codon 634, representing also the most frequent mutated codon accounting for more than 50% of MEN2A cases (7). The encoded product of *RET* consists of a membrane protein with the function of a tyrosinkinase receptor for which 4 different ligands have been described: Glial Derived Neurotrophic Factor (GDNF), Artemin, Neurturin and Persephin (63).
The PHPT phenotype is present in 20-30% of MEN2A cases carrying a mutation within codon 634. This is the most frequently described intragenic mutation site (85% of MEN2 familial cases). Every *RET* mutation at codon 634, exon 11, results in a higher incidence of PHPT and pheochromocytoma (64, 65). *In vitro* studies have demonstrated that the transforming activity related to 634 cysteine residue mutation is 3-5 fold higher than the ones at 609, 611, 618, or 620 codons (66).
Among the 634 codon mutations, it has been early described that C634R (cysteine to arginine substitution) significantly correlates to the PHPT occurrence (62), but more recently other studies failed to confirm such a correlation (67, 68). Moreover, it has been hypothesized that these mutations may exert a less transforming effect on parathyroid tissue respect to thyroid C cells (69).
Shuffenecker et al. (69) demonstrated in a population of MEN2A patients that: a) the PHPT prevalence (19.9%) did not significantly vary according to the type of 634 mutation; b) the PHPT prevalence exhibits a high interfamilial variability; c) a heterogeneity for the risk to develop PHPT exists (9%-34%); and d) PHPT could potentially represent a precocious clinical component of MEN2A syndrome: in 44% of MEN2A subjects PHPT occurred before age of 30 years [whereas it has been generally considered to occur after the third decade (53-56)]. In a clinical series they reported a 2 years old girl with a C634Y mutation (cysteine to tyrosine substitution) presenting with MTC and PHPT. All that suggests the possible existence of tissue-specific effects of *RET* mutations and, as previously reported, the thyroid C-cells could be more sensitive to RET mitogenic effect than other endocrine cell types (69).
As for the MEN1 syndrome, malignant progression of parathyroid tumors does not represent a clinical feature of MEN2A. However, a parathyroid carcinoma in a MEN2A affected individual, with combination of C634Y mutation and LOH at chromosomes 1, 2, 3p, and 16p, has been described. It has been also hypothesized that multiple allelic deletions could account for an aggressive behavior (71).

Treatment of MEN2A-PHPT manifestations

Indications and type of surgery (resection of only enlarged glands, subtotal parathyroidectomy, parathyroidectomy with autotransplantation) are similar to those in other patients with the potential for multiple parathyroid tumors, although curative resection can be less aggressive (28) (Table III). An European multicentre retrospective clinical study did consider 60 patients with MEN2A-PHPT undergone neck surgery between 1972 and 1993 (71), exhibiting a median age at diagnosis of PHPT of 38 years. PHPT resulted to be asymptomatic in more than 80% of the patients, whereas 15% clinically exhibited nephrolithiasis. Independently from the extent of resection, 94% of the patients were cured, although 13% showed persistent hypocalcemia, 3% resulted with persistent hypercalcemia, and 3% were lost in follow up. At 8-years of follow up, hypercalcemia still recurred in 12% of the patients, unrelated to the extent of parathyroid tissue resection (28). As for MEN1-PHPT, postoperative parathyroid localizing studies may be helpful if hyperparathyroidism recurs (60).

Familial Isolated PHPT (FIHPT)

FIHPT (OMIM 145000) is a rare hereditary disorder characterized by uni- or multiglandular parathyroid lesions in the absence of hyperfunction in other endocrine tissues (Table I). FIHPT is transmitted in an autosomal dominant manner (72). Few large families have been shown to be linked to *MEN1* gene (73-75), or to calcium sensing receptor (*CaSR*) gene mutations (75), while other families exhibit a segregation of phenotype with DNA markers close by the Hyperparathyroidism-Jaw tumors (HPT-JT) syndrome locus at 1q25-q32. Most of FIHPT kindreds have currently an unknown genetic background (28) (Table II). To date, approximately over 100 FIHPT families have been described (76, 77).
In deed, the clinical management of this form could be complex, although the generic surgical principles of PHPT treatment can be generally applied.

Pathology

Uni- or multiglandular involvement represents the most frequent pathological picture underlying the parathyroid hyperfunction (Table III). Progression to malignancy have not been reported for affected subjects with solitary parathyroid adenoma from two FIHPT families mapped to the same region as the HPT-JT syndrome on chromosome 1q21-q32 (78).

Molecular aspects

No gene has yet been associated exclusively with FIHPT. However, as mentioned above, FIHPT has been linked to mutations in the *MEN1*, and *CaSR* genes, whereas in some families genetic linkage to these loci was not established (28). All this is consistent with a genetic and clinical heterogeneity of this form of PHPT. Carpten et al. reported in a patient from one of the two FIHPT families mapped to chromosome 1q21-q-32, a mutation in *HRPT2* gene, confirming the they are allelic to the HPT-JT syndrome (79) (Table III).

Treatment of FIHPT manifestations

In a case of uniglandular disease, parathyroid adenomectomy can be performed, whereas for multiglandular involvement a subtotal parathyroidectomy or total parathyroidectomy, with autologous reimplantation, can be considered (Table III). Of course, FIHPT linked to mutations in *MEN1* or *HRPT2* genes should be treated similarly to MEN1- and HPT-JT-associated PHPT, respectively, since the patient may be from a kindred with absent or low penetrance of other associated tumor types (28).

Hyperparathyroidism-Jaw Tumors (HPT-JT) syndrome

HPT-JT (OMIM 607393) (80) is a rare autosomal dominantly inherited disorder characterized by fibrous-osseous tumors of mandible and/or maxilla (ossifying fibroma), Wilms' tumor, papillary renal carcinoma, polycystic kidney disease, renal cysts and PHPT. The latter exhibits an aggressive behavior within this syndrome and it is frequently sustained by parathyroid carcinoma (79, 81).
In the context of PHPT-related syndromes (Table I), HPT-JT syndrome is one of the least common and relatively unknown pictures, although not less interesting or important.
About 80% of patients present with PHPT (79), that may develop in late adolescence or older. A reduced penetrance in females has been reported (82), and parathyroid carcinoma may occur in approximately 10-15% of affected individuals (72, 79). When compared to MEN1-related PHPT, HTP-JT syndrome may run a more aggressive course: the patients tend to have more severe hypercalcemia and hypercalcemic crisis could represent the first clinical evidence. In order to monitor the presence/absence of PHPT, HPT-JT patients should undergo annual blood tests evaluating ionized calcium and intact parathyroid hormone (iPTH) levels, beginning by 15 years of age. However, it should be taken always into account, due to their possible severity, that lesions in the maxilla, mandible, kidney, and uterus should be carefully monitorized by imaging studies (i.e. orthopantography of the face, perhaps once in every 3 years, and annual abdominal ultrasound or computed tomography scan).

Pathology

PHPT in HPT-JT syndrome generally consists of involvement of one or two parathyroid glands (adenoma or double adenoma) (Table III) that may be or may be not synchronously present (78), differently from the MEN1-PHPT in which all glands are frequently involved. Parathyroid carcinoma may occur in approximately 10-15% of affected individuals (72, 79).
The high incidence of cystic figure in resected parathyroid glands represents a classical pathological feature of parathyroid neoplasia in HPT-JT syndrome. In fact, due to frequent identification of parathyroid recurring cystic adenomas this clinical entity can be referred to also as familial cystic parathyroid adenomatosis (83) (Table III). The jaw lesions typically associated to this syndrome have been reported to be histologically distinct from the typical ones representing the bone disease classically associated to PHPT (82, 84).

Molecular aspects

Very recently, the *HRPT2* gene, responsible for this syndrome, has been identified in the "tumor suppressor gene" parafibromin, previously mapped at 1q25-q32 (Table II). This gene appears to be involved also in the pathogenesis of sporadic forms of PHPT (85). Fourteen germline inactivating mutations of *HPRT2* gene were identified in 26 kindreds (79) (Table II). The gene encodes a protein of 531 amino acids, named parafibromin, involved in the development of parathyroid tumors and ossifying fibromas. To date, the protein does not exhibit any homology to known protein domains. The gene appears to be ubiquitously expressed in several human tissues such as kidney, heart, liver, pancreas, skeletal muscles, brain and lung (79). However, its role in development and tumorigenesis still remains to be elucidated.
Loss of wild-type alleles in HPT-JT syndrome was found both in renal (82) and parathyroid tumors (78, 84). These findings, together with the inactivating nature of the germline mutations strongly suggest a tumor suppressive role for parafibromin. Such LOH are not as frequent as reported in MEN1-related tumors.
To date, it has been no possible to describe a genotype-phenotype correlation and more data from other affected families and from genetic studies are necessary to possibly determine the eventual existence of such a correlation.
However, the possibility to perform DNA test provides the great opportunity for an early identification of an asymptomatic gene carrier who will receive the needed stringent clinical screening procedures.

Treatment of HPT-JT-PHPT manifestations

As soon clinical evidence of PHPT as occurred, neck surgery should be promptly performed. However, a general consensus on which type of surgical approach should be adopted, if removal of the enlarged gland with long-term follow-up or complete parathyroidectomy followed by auto-transplantation to the nondominant forearm has not been reached (86). For parathyroid carcinoma neck surgery, specifically an en bloc resection of primary tumor, is the only curative treatment (Table III). Alternatively, affected patients could undergo repetitive palliative surgical exeresis of metastatic nodules.

Familial Hypercalcemia Hypocalciuria Syndrome (FHH)/ Neonatal Severe Hyperparathyroidism (NSHPT)

FHH (OMIM 145980) (Table I) is a rare disorder inherited in autosomal dominant manner and characterized in the adult by the outcome of increased/normal levels of serum calcium, moderate hypophosphoremia, increased/normal circulating PTH levels, that are frequently inadequate when correlated to serum calcium levels and an inappropriately low urinary calcium excretion (87). The majority of patients with FHH are asymptomatic and do not benefit from surgical resection of their mildly enlarged parathyroid that cannot correct the calcium-dependent PTH secretion set-point abnormality (88, 89). FHH-related hypercalcemia is highly penetrant at all ages (90). Generally, these patients show relative hypocalciuria (urinary calcium/creatinine ratio typically <0·01) in the presence of hypercalcemia and hyperparathyroidism due to inactivation of CaSR protein in renal tubules. Moreover, a mild hypermagnesemia can be found (90, 91).
NSHPT (OMIM 239200) (Table I) generally represents the ho-

mozygous form of FHH, in which PHPT occurs at birth or within the first 6 months of life determining a severe symptomatic hypercalcemia, with skeletal manifestations of PHPT and if neck surgery is not promptly performed a lethal outcome may occur.

Pathology

PHPT in the setting of FHH is generally sustained by the presence of mildly enlarged parathyroid glands (88, 89), whereas markedly hyperplastic parathyroid glands are a typical feature of NSHPT-related PHPT (Table III).

Molecular aspects

Inactivating mutations, with a loss of function, of *CaSR* gene, localized at chromosome 3q13-21, account for both the forms (92, 93) (Table II). CaSR protein is a membrane protein consisting of 1078 amino acids, mainly expressed by kidney and parathyroid cells, belongs to the G proteins-coupled receptor (GPCR) superfamily. The CaSR is able to sense small changes in circulating calcium concentration and when activated it inhibits PTH secretion and renal tubule calcium reabsorption. The described mutations in FHH and NSHPT subjects are prevalently localized in the calcium binding site of extracellular portion of receptor. Inactivation of this GPCR protein results in half-maximal inhibition of PTH secretion only at increased concentrations of serum calcium (calcium set-point), although the magnitude of PTH suppression by increased serum calcium concentrations is normal in patients with FHH (94). Somatic mutations within the *CaSR* gene, which would explain impaired function and altered receptor expression, have not been detected both in sporadic and familial forms of parathyroid tumors thus far (95, 96).

Treatment of FHH/NSHPT-PHPT manifestations

Although it is generally accepted that FHH patients do not benefit from surgery of parathyroid lesions, subtotal parathyroidectomy can be performed in subjects developing symptomatic PHPT (Table III) who may have an underlying polyclonal parathyroid cell hyperproliferation due to a heterozygous inactivation of CaSR (28) or to another hypothetical acquired genetic defect in a different gene (97). When performed the neck surgery in FHH subjects may include subtotal parathyroidectomy leaving 10–20 mg of parathyroid tissue in order to achieve normocalcemia (Table III). In all cases, cryopreservation of parathyroid tissue should be considered (28). Total parathyroidectomy must be performed in the first months of life (98) in NSHPT affected infants (Table III).

Familial Hypercalcemia Hypercalciuria Syndrome or Autosomal Dominant Moderate Hyperparathyroidism (ADMH)

Carling et al. reported a large family with 20 members, from different generations, affected by this syndrome (OMIM 601199) (99) (Table I). These subjects did exhibit hypercalcemia and hypercalciuria, with an inappropriately high serum PTH and magnesium levels and with nephrolithiasis in a subset of patients.

Pathology

Uni-, multi-glandular involvement of parathyroid glands was found and diffuse to nodular parathyroid neoplasia has been reported on pathological examination (Table III).

Molecular aspects

DNA test revealed the presence of an atypical inactivating mutation in the intra-cytoplasmic tail domain of *CaSR* in the germline of affected subjects (Table II). LOH analysis revealed allelic losses at various genetic loci, consistent with mono- or oligoclonality of parathyroid tumors (88).

Treatment of ADMH-PHPT manifestations

Differently than classical FHH cases, radical subtotal parathyroid resection with parathyroid remnants of 10-20 mg or total parathyroidectomy with autotransplantation (Table III) normalized calcemia in 60% of affected. A persistent hypercalcemia was noted in the 60% of patients (3/5) subjected to less radical parathyroid surgical procedures. However, after an average follow up of 5.1 years no patients with recurrent hypercalcemia have been reported (28).

Conclusions

In general, an inherited hyperparathyroid syndrome should be suspected in younger patients with PHPT, <40 years old or at least two decades earlier than the sporadic counterpart, and/or in patients with multiple parathyroid adenomas or hyperplasia at surgery as seen in MEN1 or FHH syndromes, atypical parathyroid adenomas, such as familial cystic parathyroid adenomatosis, or parathyroid carcinoma as reported in HPT-JT syndrome, and in presence of a family or past medical history pointing to one of the described syndromes.

The availability of specific genetic testing for four of the syndromes has improved diagnostic accuracy and simplified family monitoring in many cases, but its current cost and limited accessibility require rationalization of its use.

Moreover, the cloning of several genes responsible for familial PHPT syndrome has increased the possibilities for new basic and clinical researches. Functional studies have to be performed to understand the function of a specific gene, as also the mechanisms by which its mutations lead to parathyroid tumorigenesis. A great help will come from the creation of specific animal models that will provide the possibility to manipulate the mouse homologue of the gene(s).

The advent of intraoperative PTH evaluation, as a routine evaluation in many centers performing parathyroid surgery, may be helpful for an optimal outcome of parathyroid surgery for familial PHPT syndromes, although some controversies are still existing concerning the rate of possible false-positive results and the possibility of inadequate resection of parathyroid tissue in patients with multiglandular disease (28, 100, 101). In order to reduce the risk of false-positive results, specially in MEN1 patients, it has been suggested to apply more stringent criteria in the threshold value of percentage reduction of PTH circulating levels prior to establish an adequate excision of parathyroid tissue (102, 103). However, further studies are needed to optimize rates of false-positive and –negative results in the setting of familial PHPT to guide an adequate extent of parathyroid tissue resection to achieve postoperative long-term eucalcemia.

Finally, new acquisitions in the pathogenesis of familial PHPT will be extremely useful to examine the role of specific genetic pathways in the sporadic counterparts. In particular, it will be important to understand how specific gene mutations, such as in *HRPT2* gene, can contribute to malignant progression in a distinct subset of parathyroid tumors. Molecular techniques such as the microarray expression profile analysis may recognize the existence of a sort of molecular

signatures distinguished for each subset of familial parathyroid tumors, also contributing to define a genotype–phenotype correlation that could improve the clinical management of this disease.

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